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Original Research

Assessment of the continuity of treatment among patients using anticholinergic medication

The treatment contuinity of anticholinergic drugs

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Abstract

Aim: The aim of this study was to identify patients started on anticholinergic therapy for the treatment of overactive bladder (OAB) and urge urinary incontinence (UUI) and examine the continuity of treatment.

Material and Methods: Patients admitted to the urology outpatient clinic between 2021 and 2022 and diagnosed with OAB and UUI were retrospectively analyzed. Age, gender, and frequency of pollakiuria and nocturia were noted. In patients who were started on anticholinergics or beta-3 adrenoceptor agonists, the number of times the active substance was changed due to side effects or failure to benefit from treatment was recorded. The rates of patients who benefited from the first anticholinergic drug and the rates of anticholinergic drug changes were investigated.

Results: The mean patient age was 56.88 years (19–89 years). A total of 197 patients (50 males and 147 females) were evaluated. The mean frequency of pollakiuria and nocturia was 10.64 (7–20) and 2.89 (1–7), respectively. While 64.5% (n = 127) of the patients had no comorbidity, 16.2% had diabetes mellitus and 13.2% had hypertension. The rate of satisfaction with the first medication and continuation of treatment was 50.2% (n = 99) in all patients, regardless of the active substance. Of the remaining patients, 36.5% (n = 72) switched to the second active substance, 10.6% (n = 21) switched to the third active substance, and 5.23% (n = 5) switched to the fourth active substance.

Discussion: Anticholinergic agents play an important role in the medical treatment of patients with UUI and OAB, which are common in the general population. Patients who start treatment may discontinue owing to a lack of benefits or side effects. Therefore, patients who are started on treatment should be called in for frequent follow-ups, and continuity of treatment should be ensured with appropriate drug selection.

Keywords

Anticholinergics, Overactive Bladder, Urge Incontinence

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Introduction

Overactive bladder (OAB) is characterized by frequent urination and sudden urinary sensations with or without urinary incontinence. Urge urinary incontinence (UUI) has been defined by the International Society of Urogynecology and the International Continence Society as a sudden, compelling urge to urinate that is difficult to postpone (available at: https://www.auanet.org/guidelines).

OAB and UUI affect people's quality of life and may cause them to withdraw from social life. They also significantly affect daily functioning and productivity. Furthermore, symptoms of depression are increased in these patients [1].

The main goal in the treatment of OAB and UUI is to improve the quality of life by reducing the occurrence and severity of symptoms. Lifestyle changes (constipation, obesity, and smoking) and pelvic floor muscle exercises are recommended before pharmacologic treatment. Pharmacologic treatment is recommended for patients who do not benefit from these treatments [2].

Anticholinergic therapy is the first-line treatment option for patients with OAB. There are different drugs such as oxybutynin, propiverine, solifenacin, tolterodine, darifenacin, and trospium chloride with well-defined pharmacotherapy. Oxybutynin has antimuscarinic and direct muscle relaxant properties. Propiverine has both calcium modulating and anticholinergic properties. Darifenacin, solifenacin, tolterodine, and trospium chloride are pure antimuscarinics. The most common side effects of all antimuscarinic drugs are dry mouth, constipation, fatigue, pruritus, and acute urinary retention, with varying degrees of side effects according to the agent.

The International Consultation on Incontinence has rated anticholinergics as 1 (the best possible) for "level of evidence" and A (the best possible) for "level of recommendation" because of the well-documented effects of these drugs on detrusor overactivity and their favorable treatment and side effect profiles [3].

Anticholinergics and beta-3 adrenergic receptor agonists have been used as long-term second-line drugs for OAB and UUI. The effects of these drugs are delayed. Therefore, using them for at least 1 and up to 3 months is recommended to evaluate the response [2].

Although there are studies reporting that some anticholinergic drugs are superior to others, the main body of evidence in the literature suggests that these drugs are not superior to each other [4]. Therefore, the patient's age, comorbidities, cost, and physician preference play important roles in determining which drug to start treatment with. Based on these considerations, the aim of this study was to identify anticholinergic drugs frequently used in patients with OAB and UUI and to evaluate treatment continuity.

Material and Methods

Patients admitted to the urology outpatient clinic between January 2021 and December 2021 and diagnosed with OAB and UUI were retrospectively analyzed. Age, gender, and frequency of pollakiuria and nocturia were noted. After 3 months of anticholinergic or beta-3 adrenoceptor agonists use, the rates of treatment continuation and active substance change were noted. Patients under 18 years of age, those with mixed or stress incontinence, those receiving medical treatment for less than 3 months, and patients with a history of surgery were excluded from the study.

Ethical Approval

Ethics Committee approval for the study was obtained.

Results

The mean patient age was 56.88 ± 15.79 years (19–89 years). The male/female ratio was 50/147 (25.4% male and 74.6% female). Among the patients included in the study, 64.5% (n = 127) had no comorbidity, 16.2% had diabetes mellitus, 13.2% had hypertension, 3% had chronic obstructive pulmonary disease, 1% had asthma, 1% had migraines, and 1% had Parkinson's disease. The mean frequency of pollakiuria and nocturia was 10.64 ± 2.65 (7–20) and 2.89 ± 1.4 (1–7), respectively. Demographic data of the patients are summarized in Table 1.

All drugs were administered orally. When the total efficacy of the first-line drugs was analyzed, it was found that 99 patients (50.2%) were satisfied with the treatment and continued using their medications. Of the remaining patients, 36.5% (n = 72) switched to the second active substance, 10.6% (n = 21) switched to the third active substance, and 5.23% (n = 5) switched to the fourth active substance.

Based on the active substance, 12.1% of the first-line drugs initiated were "oral oxybutynin 5 mg" (n = 24), 36% were "solifenacin 5 mg" (n = 71), 13.1% were "tolterodine 4 mg" (n = 26), 8.1% were "propiverine 30 mg" (n = 16), 4% were "darifenacin 15 mg" (n = 8), 8.1% were "trospium 30 mg" (n = 16), and 18.2% were "mirabegron 50 mg" (n = 36).

When each drug was evaluated individually, it was found that only 4 (16.6%) of 24 patients who were started on oxybutynin responded to the first-line treatment and continued with the drug, while 8 (75%) patients switched to the second drug and 2 (8.3%) switched to the third drug. Among the 71 patients who were started on solifenacin, 51 (71.8%) were satisfied with the first-line treatment, while 20 (28.2%) switched to the second or third drug. The rate of patients benefiting from first-line

Table 1. Demographic Data

Patient Characteristics	
Age (Years, mean ± SD, min–max)	56,88 ± 15,79 (19-89)
Gender n, (%)	
Male	50 (25.4)
Female	147 (74.6)
Comorbidity n, (%)	
No	127 (64.5)
Diabetes mellitus	32 (16.2)
Hypertension	26 (13.2)
Chronic obstructive pulmonary disease	6 (3)
Asthma	1 (1)
Migraine	1 (1)
Parkinson's disease	1 (1)
Micturition frequency (number, mean ±SD, min–max)	
Pollakiuria	10.64 ± 2.65 (7-20)
Nocturia	2.89 ± 1.4 (1-7)

Table 2. Percentage of Drug Changes by Active Substance

	First active substances started and number of patients N, %	Number of patients who benefited from the first active substance and continued treatment N, (%)	Number of patients who benefited from the second active substance and continued treatment N, (%)	Number of patients who benefited from the third active substance and continued treatment N, (%)	Number of patients who benefited from the fourth active substance and continued treatment N, (%)
Oxybutynin 5 mg	24, (100)	4, (16,6)	18, (75,0)	2 (8,3)	0, (0)
Solifenacin 5 mg	71, (100)	51, (71,8)	16 (22,5)	4, (5,6)	0, (0)
Tolterodine 4 mg	26, (100)	14 (53,8)	6 (23,0)	6, (23,0)	0, (0)
Propiverine 30 mg	16, (100)	2, (12,5)	6 (37,5)	6, (37,5)	2, (12,5)
Darifenacin 15 mg	8, (100)	4, (50,0)	4, (50,0)	0, (0)	0, (0)
Trospium 30 mg	16, (100)	6, (37,5)	6, (37,5)	2, (12,5)	2, (12,5)
Mirabegron 50 mg	36, (100)	18, (50)	16, (44,4)	1, (2,7)	1, (2,7)
Total	197 (100)	99 (50,2)	72 (36,5)	21 (10,6)	5 (2,53)

treatment was 53.8% (n = 14) for tolterodine, 12.5% (n = 2) for propiverine, 50% (n = 4) for darifenacin, 37.5% (n = 6) for trospium, and 50% (n = 18) for mirabegron, and these patients did not need to change the active substance. The total number of patients and the number of drug changes based on active substances are shown in Table 2.

Discussion

OAB and UUI affect the quality of life and cause problems in social life. Changes such as fluid restriction, lifestyle modification, cessation or reduction of caffeine and alcohol intake, and weight loss as first-line treatments for OAB and UUI are beneficial in alleviating the symptoms. Pelvic floor muscle exercises have also been shown to reduce symptoms. It has been shown that the frequency of weekly UUI decreased in obese patients who lost weight [2].

Pharmacologic treatment is recommended for patients who do not benefit from these treatment options. Anticholinergics and beta-3 adrenoceptor agonist are the drugs used for pharmacologic treatment.

The mechanism of action of anticholinergics in the treatment of OAB and UUI is to decrease bladder contractions, decrease urges, and increase bladder capacity by blocking muscarinic receptors in the detrusor muscle [5].

The beta-3 adrenoceptor agonist is found in the detrusor muscle and, when stimulated, relaxes the detrusor muscle, resulting in increased bladder capacity [6].

Oxybutynin is one of the oldest agents used in the treatment of OAB and UUI. Oxybutynin also has a local anesthetic effect because of its direct spasmolytic and lidocaine-like effects. In a review of 15 randomized controlled trials of oxybutynin IR, 52% of patients reported improvement in incontinence and 33% reported a decrease in urination frequency. Several studies reported that the efficacy of oxybutynin IR was “very good,” but side effects such as constipation, headache, and dry mouth were observed in more than 50% of the patients [7]. In another study, improvement in incontinence was observed in 23% of patients receiving oxybutynin for 12 weeks [8]. In the present study, it was found that 16% of patients who were started on oxybutynin benefited from the treatment and no drug change was needed. Because the number of patients started on oxybutynin as first-line therapy in the present study was small, a fair comparison with the literature could not be made.

Solifenacin is a selective M1–M3 receptor antagonist. In four separate phase III studies, improvement in incontinence was observed in 52% of patients who used solifenacin for 12 weeks and a decrease in urges was observed in 50% of the patients [9]. In the present study, 71% of patients who were started on solifenacin benefited from the treatment and no drug change was needed. These findings on efficacy and treatment continuity are consistent with the literature.

Tolterodine, the first selective antimuscarinic, binds to M1 and M3 receptor subtypes competitively and at similar rates. Although it is a non-selective antimuscarinic agent, animal experiments show that it exhibits organ-specific selectivity to M2 and M3 muscarinic receptors in the bladder. A 10-week double-blind, randomized trial was conducted in 378 patients with OAB to compare tolterodine and oxybutynin. The rate of improvement in urinary symptoms was 45% for tolterodine and 41% for oxybutynin [10]. In the present study, 53.8% of patients who were started on tolterodine benefited from the treatment and no drug change was needed. This finding is consistent with the literature.

Propiverine is a molecule that can be used safely in neurogenic or non-neurogenic detrusor overactivity all age groups. In a randomized, controlled, double-blind study published in 2005 comparing propiverine and tolterodine, the efficacy of propiverine was rated as “very good” in 19 cases (26.0%), “good” in 25 cases (34.2%), “moderate” in 21 cases (28.8%), and “inadequate” in 8 cases (10.9%) [11]. In the study conducted by Madersbacher et al., 63% of the patients showed improvement in symptom scores, consistent with increased bladder capacity and favorable urodynamic findings. In the same study, 23% of the patients in the placebo group also reported improvement [12]. In the present study, 12.5% of patients benefited from propiverine as the first-line treatment. In our opinion, the most important reason for this rate being lower than that reported in the literature is the small number of patients started on propiverine and possible patient-related deficiencies in drug use.

Darifenacin is a molecule that inhibits detrusor smooth muscle with a direct antimuscarinic effect without a calcium antagonist and has a high affinity for the M3 receptor. In a multicenter, randomized, placebo-controlled, double-blind study published by Haab et al. in 2004, darifenacin 7.5 mg and 15 mg were significantly superior to placebo in terms of improvements in voiding frequency, bladder capacity, frequency of urge to void, severity of urge to void, and the number of

incontinence episodes leading to changes in clothing or pads. It was found that incontinence episodes decreased by 67.7% with darifenacin 7.5 mg and by 72.8% with darifenacin 15 mg [13]. In another similarly designed study involving 1059 patients, 12 weeks of darifenacin treatment resulted in a significant reduction in the median (% change, interquartile range) number of incontinence episodes per week compared to baseline (7.5 mg darifenacin −8.8%–−68.4%, −15.1–−4.4) (15 mg darifenacin −10.6%–−76.8%, −17.3–−5.8) [14]. In the present study, 50% of the patients who were started on darifenacin were satisfied and continued with the treatment at the 12-week follow-up. Trospium chloride (Trospium) is a quaternary ammonium derivative; therefore, it shows significantly lower penetration through the blood–brain barrier than other more lipophilic antimuscarinic agents. In the study by Staskin et al. (2010), trospium was not detected in the cerebrospinal fluid during the peak plasma concentrations in patients receiving 60 mg of trospium daily for more than 10 days [15]. Trospium has a high affinity for each of the muscarinic receptor subtypes. In terms of effect, randomized studies have shown that trospium improves urodynamic and symptomatic parameters in patients with OAB [16, 17]. Zinner et al. found that 20 mg of trospium twice a day significantly reduced the average frequency of micturition and UUI episodes compared to placebo [18]. In another multicenter, randomized, double-blind, placebo-controlled phase III study, 601 patients with OAB were treated with 60 mg of trospium once daily, and it was found that daily urinary frequency, daily urge incontinence episodes, urgency severity, and number of urgent voids per day significantly improved compared to placebo in weeks 1–12 [19]. In the present study, it was found that 37.5% of the patients who were started on trospium as the first-line drug had improvement in UUI and OAB symptoms and the patients continued treatment.

Beta-3 adrenoceptors exert their effects by activating adenylyl cyclase via cAMP, resulting in detrusor relaxation. The role of beta-3 adrenoceptors in urothelial cells and sensory fibers remains unclear. A study demonstrated beta-3 adrenoceptor expression in the cholinergic nerve endings of the detrusor and suggested that this receptor plays a role in the modulation of acetylcholine release [20]. Mirabegron is the first beta-3 adrenoceptor agonist to be approved by the FDA and EMA. In a study using mirabegron, it was shown that patients who used mirabegron for 4 weeks had a 50% reduction in urinary incontinence compared with placebo, and this effect continued for 12 weeks [21]. In the present study, it was found that 50% of the patients who were started on mirabegron benefited from the treatment and no drug change was needed. This finding is consistent with the literature.

Limitations of the present study include the small number of patients, the exclusion of drug side effects because they were not recorded in patient data, the lack of symptom scores for UUI and OAB symptoms compared before and after treatment, and the retrospective design of the study.

Conclusion

Anticholinergic agents play an important role in the medical treatment of patients with UUI and OAB, both of which are common in the general population. Patients who start treatment may discontinue because of a lack of benefit or side effects. Therefore, patients receiving treatment should be called in for frequent follow-ups, and treatment continuity should be ensured through appropriate drug selection for individual patients.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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Conflict of interest

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